Remarks/Arguments

Claims 5, 7, 9, 11 and 13-20 are pending in the present application. Claims 1-4 have been withdrawn. Claim 9 has been amended to correct dependency.

I. Rejection of Claims 5, 7, 9, 11 and 13-20 Under 35 USC § 103(a) Over Wada et al.

Claims 5, 7, 9, 11 and 13-20 are rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over Wada *et al.* The Examiner states that Wada teaches use of a compound encompassed by the generic formula of claim 5 and further discloses that the compound is useful in the treatment of seizures associated with epilepsy. The Examiner concludes, therefore, that it would have been obvious to one of ordinary skill in the art to modify Wada's teachings of research results with an experimental rat model of seizures to use with humans.

Applicants respectfully disagree with the Examiner's conclusion.

Wada teaches that administration of the compound, CPBG, to rats "increases the duration of fully kindled seizures and facilitates the developmental seizure process. . .." In other words, administration of CPBG to rats **causes seizures** in this animal model. Wada further states that *m*-CPBG caused a significant reduction in the experimental stimulations needed to **produce seizures and significantly increased the duration of seizures**. The authors concluded that "*m*-CPBG increases the duration of fully kindled seizures and facilitates the developmental seizure process." Clearly, this reference cannot be read as suggesting the use of agmatine or its analogs in the treatment of human epilepsy. Instead, it clearly **teaches away** from the use of agmatine to treat seizures of any type. As such, this reference should be removed as prior art to the claimed invention.

The Examiner also asserts that Wada differs from the claimed invention in the specific dosage regimen, but that the determination of optimum proportions or amounts iss considered to be within the skill of the art. Applicant submits that this is not the case with drugs to treat epilepsy and encloses a published scientific article (Del-Bel et al., Braz. J. Med. Biol. Res., 1997, 30(8):971-979) as evidence of this. The enclosed article is directed to a study of the effects of a NOS inhibitor (L-NOARG) on seizure induction by drugs and sound in various animal models. The results show that "the effects of NOS inhibition and consequently the inhibition of NO synthesis on seizure activity depend on the seizure model (sensory or chemical) and, in the case of chemical induction, on the type and dose of the convulsant drug." The enclosed article demonstrates that the selection of the dosage of a particular drug to treat epilepsy is not a merely a matter of optimization. The article by Del-Bel demonstrates that at one dose a drug can induce seizures, while at another dose the same drug protects against seizures. In the light of Del-Bel's teachings, not only is Wada's study irrelevant because it addresses auditory-induced seizures and because Wada et al. conclude that the effects observed in their studies "may differ depending on seizure models" (Wada et al. p. 315), but the dosage of drug used by Wada cannot simply be extrapolated for use in humans as suggested by the Examiner.

Accordingly, the rejection of claims 5, 7, 9, 11 and 13-20 are rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over Wada *et al.* is respectfully traversed.

II. Rejection of Claims 5, 7, 9, 11, and 13-20 Under 35 U.S.C. § 103(a) Over Uzbay *et al.* and Rajasekaran

Claims 5, 7, 9, 11, and 13-20 are rejected under 35 U.S.C. § 103(a) over Uzbay *et al.* and Rajasekaran. The Examiner states that Uzbay teaches use of 40 mg to effectively treat audiogenic seizures associated with alcohol withdrawal (in rats). The Examiner also relies on Uzbay as teaching that the therapeutic effects in rats is due to blocking NOS and the NMDA

subclass of glutamate receptor channels. The examiner relies on Rajasekaran as teaching anticonvulsant activity of agmatine in the treatment of seizures due to epilepsy and that the underlying mechanism for the anticonvulsant activity is NO inhibition. The Examiner concludes therefore, that it would have been obvious to modify Uzbay's teaching in view of Rajasekaran to treat seizures due to epilepsy.

Applicant respectfully disagrees with the Examiner's conclusion. The teachings of Uzbay *et al.* are clearly limited to and relevant only to ethanol withdrawal syndrome associated. In particular, this reference teaches that agmatine

> "reduced, dose-dependently and significantly, the intensity of stereotyped behavior and incidence of wet dog shakes and tremors appearing during the ethanol withdrawal."

[p. 155, § 3.3]. However, the reference goes on to disclose agmatine

> "reduced both incidence and intensity of the audiogenic seizure appearing at the 6th h. of ethanol withdrawal, dose-dependently (Table 2), **but the inhibitory effect of agmatine did not reach a statistically significant level**."

[p.155, § 3.3]. Clearly, these authors did not conclude that agmatine is useful for treatment of audiogenic seizures as the Examiner asserts. These authors concluded that agmatine is useful for treating the syndrome of ethanol withdrawal, but that it has no significant effect on seizures associated with ethanol withdrawal.

The Examiner asserts that Uzbay et al. teach "that the therapeutic effects [of agmatine] are resulted from blocking nitric oxide synthesis and selective inhibition of the NMD subclass of glutamate receptor channels." However, the authors actually state that the inhibitory effects of agmatine on ethanol withdrawal syndrome may be explained by any of three different mechanisms and they do not speculate as to which of the various mechanisms come into play in

the treatment of ethanol withdrawal syndrome. [p. 156] Contrary to the examiner's assertions, these authors did not conclude that the therapeutic effect of agmatine on ethanol withdrawal syndrome is through inhibition of NMD. Certainly, they did not speculate about mechanisms of action concerning the effects of agmatine on seizures associated with ethanol withdrawal syndrome, since **their data show that there was no statistically significant effect on seizures**. The Examiner also states that the secondary reference, Rajasekaran et al., "teaches the anticonvulsant activity of agmatine used in the treatment of seizure due to epilepsy" and teaches that the underlying mechanism for anticonvulsant activity is "utilizing NO inhibition, where NO is produced in the neurons in response to activation by NMD receptors." However, Rajasekaran et al. did not address the effects of agmatine on convulsions, but instead tested only the prodrug, L-arginine (L-arg). These authors concluded that the effects of L-arg "may be direct, or a product of its metabolism such as agmatine or to the possible accumulation of L-arsenine per se." This is the only mention of agmatine in the cited reference and it is purely speculative. No data concerning agmatine was shown in the secondary reference, and no conclusions about its effect on seizures were offered. Since there are no data in this reference demonstrating that agmatine is the active metabolite of L-argenine, this disclosure is merely a suggestion to try agmatine, and does not provide a reasonable expectation of success should agmatine be used to treat epilepsy, as is required under 35 U.S.C. § 103. *See Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d .469, 5 USPQ1529 (Fed. Cir. 1988).

The Examiner also asserts that the therapeutic affects of agmatine result "from blocking nitric oxide synthesis and selective inhibition of he NMD subclass of glutamate receptor channels" although the authors of the primary reference only propose this mechanism as one of

several possible mechanisms of action of agmatine. The Examiner has offered no evidence that the proposed mechanism of action is indeed valid. In fact, Applicant encloses herewith a published article that demonstrates that "the effects of NOS inhibitors vary with the model of seizure." (Del-Bel et al.). Thus, the Examiner's reliance on proposed mechanisms of actions, and selection of a single mechanism from three possibilities proposed by the authors of the primary reference is misplaced and does not demonstrate obviousness of the claimed invention. If the authors of the primary action are not certain of the mechanism of action of agmatine, it is unclear how the examiner can be certain.

The combination of the two cited references does not teach or suggest the claimed invention. First, as discussed above, the primary reference teaches away from the use of agmatine to treat seizures associated with alcohol withdrawal, and therefore cannot possibly be construed to suggest the use of agmatine to treat seizures associated with epilepsy. The authors themselves stated that the data relating to seizures obtained with agmatine was not statistically significant, which means that in these studies agmatine was not effective in treating seizures. Further, the primary reference does not provide the mechanism of action of agmatine as asserted by the Examiner, but merely suggests several possibilities. However, regardless of which of the various proposed mechanisms of actions of the drug proffered by the authors is correct (if any), the data presented in the primary reference clearly show that agmatine is not effective in treating seizures and one of ordinary skill in the art would recognize from the authors' conclusion that agmatine is not an effective treatment for seizures.

The secondary reference does not cure the insufficiencies of the primary reference. Rajasekaran merely suggests that the anticonvulsant activity of L-arg may be effected through agmatine, but offers no evidence to that effect. This reference can be interpreted, at best, as a

suggestion to try agmatine as an anticonvulsant, but there is no indicia of an expectation of success in the cited reference, as required under 35 U.S.C. § 103. Moreover, in view of the data set forth in the primary reference cited by the examiner, the combination of prior art suggests that anticonvulsive activity is not effected through agmatine. Thus, the combination of prior art cited by the Examiner does not establish a *prima facie* case of obviousness.

Accordingly, the rejection of claims 5, 7, 9, 11 and 13-20 under 35 USC § 103(a) is respectfully traversed.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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Date: November 7, 2005